Review Article

MODERN RADIOLOGICAL DIAGNOSTIC METHODS FOR ORAL MUCOSAL MELANOMA: RECENT ADVANCES AND FUTURE PERSPECTIVES

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ABSTRACT

Oral mucosal melanoma (OMM) is a rare and aggressive malignancy with a poor prognosis and high metastatic potential. Its subtle clinical presentation and diagnostic challenges often result in late-stage detection, complicating treatment. Advanced imaging techniques, such as PET and MRI, have significantly improved staging accuracy. Additionally, noninvasive methods and molecular profiling show promise for early detection and personalized treatments. Surgical resection remains the cornerstone of treatment, complemented by radiotherapy, including carbon-ion therapy, and systemic therapies like as immune checkpoint inhibitors and targeted therapies. Emerging approaches, such as gene therapy, adoptive cell transfer, and combination treatments, aim to enhance therapeutic outcomes. Multidisciplinary care is crucial to address the complex needs of patients, balancing oncologic control with functional and aesthetic considerations. Despite these advancements, outcomes remain poor, underscoring the urgent need for further research into the molecular mechanisms of OMM and innovative therapeutic strategies. Collaboration across research and clinical disciplines is key to driving progress and enhance patient outcomes.

Key words: Oral mucosal melanoma (OMM), Diagnostic imaging, Molecular profiling, Immunotherapy, Carbon-ion radiotherapy, Multidisciplinary oncology.

Introduction

Oral mucosal melanoma (OMM) is a rare and aggressive form of melanoma that occurs in the mucous membranes of the oral cavity. Unlike cutaneous melanoma, which is more common and well-studied, OMM presents unique challenges in diagnosis and management due to its rarity, aggressive behavior, and poor prognosis. This review includes recent advancements in understanding, diagnosing, and treating OMM, providing an in-depth overview of current trends and future directions.

Epidemiology and clinical features

Epidemiology

Mucosal melanoma represents a small fraction of all melanoma cases, with oral mucosal melanoma being even rarer. The incidence of mucosal melanoma is estimated to be 1.4 cases per million people per year, with OMM comprising only a small subset of these cases. The disease predominantly affects individuals over the age of 60, although it can occur at any age. There is no significant gender predilection, with both males and females equally affected [1-5].

Clinical presentation

Clinically, OMM often presents as a pigmented lesion in the oral cavity, commonly affecting the palate and gingiva. Symptoms may include bleeding, pain, or ulceration, although some lesions are asymptomatic and discovered incidentally during routine dental examinations [6-9]. The aggressive nature of OMM is attributed to its high propensity for local invasion and distant metastasis at the time of diagnosis [2, 10-12]. Early-stage OMM may present as a small, darkly pigmented macule or nodule, which can easily be mistaken for benign lesions such as melanotic macules or amalgam tattoos. As the disease progresses, the lesions often become more extensive, ulcerated, and symptomatic [13-16].

Clinical staging

Staging of OMM follows the American Joint Committee on Cancer (AJCC) TNM classification, which considers tumor size (T), nodal involvement (N), and distant metastasis (M). Early-stage OMM (T1-T2) is confined to the mucosal surfaces, while advanced stages (T3-T4) indicate deeper tissue invasion or extension to adjacent structures. Regional lymph node involvement and distant metastasis significantly worsen the prognosis [13, 17-19].

Diagnostic challenges

The diagnosis of OMM can be challenging due to its rarity and the nonspecific nature of early symptoms. A high index of suspicion is necessary, especially for pigmented lesions in the oral cavity that do not heal or change over time. Histopathological examination remains the gold standard for diagnosis, often supplemented by immunohistochemical staining to differentiate from other pigmented lesions such as melanotic macules or amalgam tattoos [7, 13, 20-22].

Diagnostic techniques

Early detection and accurate diagnosis are crucial for improving prognosis. However, due to the subtle initial presentation, many cases are diagnosed at an advanced stage. This underscores the importance of routine oral examinations and prompt biopsy of suspicious lesions [23, 24]. Recent advancements in imaging techniques, including positron emission tomography (PET) and magnetic resonance imaging (MRI), have improved the accuracy of staging and detection of metastases, aiding in the comprehensive management of OMM [3, 25-27].

Histopathologically, OMM is characterized by the proliferation of atypical melanocytes within the basal layer of the epithelium and invasion into the underlying connective tissue. Immunohistochemical markers, such as S-100, HMB-45, and Melan-A, are useful in confirming the diagnosis and differentiating OMM from other pigmented lesions and tumors [13, 28-30].

Noninvasive diagnostic methods

Noninvasive diagnostic methods are advancing rapidly, offering promise for early detection. Techniques such as liquid biopsies and advanced imaging modalities like PET-CT and MRI can provide detailed information about the size, location, and extent of the tumor, helping to guide treatment decisions and monitor disease progression. Combining imaging data with genetic and molecular profiling can offer a comprehensive view of the tumor, enabling more precise and personalized treatment approaches [23, 31-33].

Treatment approaches

Surgical management

Surgery remains the primary treatment modality for OMM. The goal is complete surgical excision with clear margins, which can be challenging given the anatomical constraints of the oral cavity. Achieving negative margins is critical to reduce the risk of local recurrence [1, 34-37]. Advanced surgical techniques and careful preoperative planning are essential to balance oncologic control with functional and aesthetic outcomes. In cases where surgical resection is not feasible, adjuvant therapies play a significant role [1, 35, 37].

Surgical resection often involves wide local excision, sometimes requiring complex reconstructive procedures to restore function and aesthetics. Margins of 1-2 cm are generally recommended, although the extent of resection must be individualized based on tumor size, location, and involvement of adjacent structures. Sentinel lymph node biopsy is often performed to assess regional lymph node involvement [1, 35, 37].

Radiotherapy

Radiotherapy, particularly carbon-ion radiotherapy, has shown promise in the management of OMM. Studies have demonstrated improved local control and survival rates with this modality, highlighting its potential as an adjunct or alternative to surgical intervention in select cases [3, 23, 38, 39]. Carbon-ion radiotherapy offers the advantage of delivering high doses of radiation with precision, minimizing damage to surrounding healthy tissues. This technique has shown superior outcomes compared to conventional radiotherapy, particularly in unresectable or recurrent cases [3, 22, 23, 40].

Radiotherapy is also used as adjuvant treatment to reduce the risk of local recurrence following surgery. In cases where surgery is not feasible due to the location or extent of the tumor, radiotherapy can be used as a primary treatment modality. The combination of radiotherapy with other treatments, such as chemotherapy or immunotherapy, is being explored to enhance treatment efficacy [3, 23, 41-43].

Medical oncology

The role of systemic therapy in OMM is evolving, with recent advances in immunotherapy and targeted therapy offering new hope for patients with advanced disease. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have shown efficacy in cutaneous melanoma and are being investigated for their potential in mucosal melanoma [2, 24, 44-47]. Additionally, targeted therapies against specific genetic mutations present in melanoma cells are currently being studied, aiming to improve outcomes for patients with metastatic disease [13, 24, 48, 49].

Immunotherapy

Immune checkpoint inhibitors, such as anti-PD-1 (nivolumab and pembrolizumab) and anti-CTLA-4 (ipilimumab) antibodies, have revolutionized the treatment of melanoma by enabling the immune system to target cancer cells. These therapies have shown promising results in mucosal melanoma, although their efficacy appears to be somewhat lower compared to cutaneous melanoma. Combination therapies involving checkpoint inhibitors are being explored to enhance response rates and overcome resistance [2, 24, 34, 50, 51].

Targeted therapy

Advances in molecular biology have identified specific genetic mutations in melanoma cells that can be targeted with precision therapies. For example, mutations in the KIT, NRAS, and BRAF genes are being studied for their potential as therapeutic targets in OMM. Drugs such as imatinib, which targets KIT mutations, and BRAF inhibitors like vemurafenib, are under investigation in clinical trials [24, 37, 52-54].

Chemotherapy

Although less effective than newer treatments, chemotherapy remains a treatment option for OMM, particularly in cases where other therapies are not suitable. Agents such as dacarbazine, temozolomide, and platinum-based drugs have been used, often in combination with other treatments. However, the response rates to chemotherapy in

OMM are generally low, and the focus is shifting towards more targeted and immunotherapeutic approaches [7, 12, 24, 55, 56].

Emerging treatment strategies

Current research is focused on understanding the molecular and genetic landscape of OMM to develop more effective treatments. Novel approaches, including combination therapies and personalized medicine based on genetic profiling, are under investigation [2, 37, 57]. These strategies aim to enhance the response to treatment and improve overall survival rates. Advances in molecular biology have identified potential therapeutic targets, such as mutations in the KIT, NRAS, and BRAF genes, which are being exploited in clinical trials [2, 13, 37, 58].

Moreover, advancements in gene therapy, adoptive cell transfer, and vaccine-based therapies are on the horizon, offering potential breakthroughs in the management of OMM. These innovative treatments aim to harness the body's immune system to target and destroy melanoma cells, providing a new avenue for combating this aggressive malignancy [1, 13, 37, 59].

Adjuvant and neoadjuvant therapies

Adjuvant therapies, administered after primary treatment, aim to eliminate residual disease and reduce the risk of recurrence. Neoadjuvant therapies, given before primary treatment, can shrink tumors, making them easier to remove surgically. Both strategies are being investigated in the context of OMM to optimize treatment outcomes. For instance, the use of immunotherapy or targeted therapy as neoadjuvant treatment is being studied for its potential to improve surgical outcomes and reduce metastasis [3, 24, 37].

Multidisciplinary approach

The management of OMM requires a multidisciplinary approach involving oncologists, surgeons, radiologists, pathologists, and other healthcare professionals. Regular multidisciplinary team meetings are essential to discuss individual cases and develop personalized treatment plans. This collaborative approach ensures that all aspects of the disease are addressed, including tumor resection, adjuvant therapies, reconstruction, and supportive care [6, 7, 12].

Supportive care

Supportive care plays a crucial role in the management of patients with OMM. This includes pain management, nutritional support, and psychological counseling to address the physical and emotional challenges associated with the disease. Multidisciplinary care involving oncologists, surgeons, radiologists, pathologists, and support staff is essential to provide comprehensive care and improve the quality of life for patients [3, 12, 23].

Quality of life considerations

The aggressive nature of OMM and the extensive treatments required can significantly impact patients' quality of life. Functional impairments, such as difficulties in speaking, chewing, and swallowing, are common, especially following surgical resection. Aesthetic concerns and the psychological burden of a cancer diagnosis also affect patients' well-being. Comprehensive rehabilitation, including speech therapy, physiotherapy, and psychological support, is essential to help patients cope with these challenges and improve their overall quality of life [3, 12, 37].

Prognosis and follow-up

The prognosis for OMM remains poor, with five-year survival rates ranging from 15% to 30%, depending on the stage at diagnosis and the success of initial treatments. Factors influencing prognosis include tumor thickness, presence of ulceration, and the extent of local and distant metastasis [2, 3, 13]. Regular follow-up is essential for early detection of recurrence or metastasis. This typically involves clinical examinations, imaging studies, and, in some cases, biopsy of suspicious lesions. Lifelong surveillance is recommended due to the high risk of late recurrence and secondary malignancies [13, 24, 60].

Prognostic factors

Several factors influence the prognosis of patients with OMM. Tumor thickness and ulceration are significant predictors of outcome, with thicker and ulcerated tumors associated with a worse prognosis. The involvement of regional lymph nodes and the presence of distant metastasis at diagnosis are also critical factors affecting survival. Histopathological features, such as mitotic rate and lymphovascular invasion, provide additional prognostic information [2, 12, 13].

Long-term follow-up

Long-term follow-up is essential for detecting recurrences and managing complications related to treatment. Follow-up protocols typically involve regular clinical examinations, imaging studies, and, when necessary, biopsies of suspicious lesions. Given the high risk of late recurrence and the potential for secondary malignancies, lifelong surveillance is recommended. Follow-up intervals may vary based on the initial stage of the disease and the treatments administered, but regular monitoring is crucial for timely intervention [12, 13, 61].

Research and future directions

Research into the molecular and genetic basis of OMM is ongoing, to identify novel therapeutic targets and improve treatment outcomes. Genomic studies have revealed distinct genetic alterations in mucosal melanoma compared to cutaneous melanoma, providing insights into potential mechanisms of resistance and opportunities for targeted therapies [2, 37, 62].

Clinical trials

Participation in clinical trials is encouraged for patients with

OMM, as this provides access to new and potentially more effective treatments. Current clinical trials are investigating various aspects of OMM management, including the efficacy of novel immunotherapies, targeted therapies, and combination treatments. Clinical trials also play a critical role in advancing our understanding of the disease and identifying biomarkers that can predict treatment response [14, 24, 37].

Personalized medicine

Personalized medicine, based on genetic profiling of tumors, is an emerging approach in the management of OMM. By tailoring treatment strategies to the specific genetic alterations present in a patient's tumor, personalized medicine aims to improve treatment efficacy and reduce adverse effects. This approach involves comprehensive molecular analysis of tumor samples to identify specific mutations and guide therapy selection [17, 24, 37].

Translational research

Translational research, which bridges the gap between laboratory discoveries and clinical applications, is essential for developing new treatments for OMM. Studies focusing on the tumor microenvironment, immune evasion mechanisms, and resistance pathways provide valuable insights that can be translated into novel therapeutic strategies. Collaboration between researchers, clinicians, and pharmaceutical companies is crucial to accelerate the development of effective treatments [2, 20, 37].

Conclusion

Oral mucosal melanoma remains a challenging malignancy with a poor prognosis. Early diagnosis, aggressive surgical management, and advancements in radiotherapy and systemic therapies are critical to improving outcomes. Ongoing research and clinical trials are essential to develop more effective treatments and ultimately improve survival rates for patients with this aggressive disease. Collaboration between oncologists, surgeons, radiologists, and researchers is paramount in advancing the understanding and management of OMM. As our knowledge of the molecular underpinnings of OMM expands, there is hope for the development of more targeted and effective therapies, ultimately leading to better outcomes for patients affected by this rare and aggressive malignancy.

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